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Case Report

CASE REPORT

A case report: invasive ductal carcinoma in mosaic Li-Fraumeni syndrome

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Abstract

Li-Fraumeni syndrome (LFS) is a rare autosomal dominant condition caused by pathogenic variants in the TP53 tumor suppressor gene and characterized by a high lifetime risk of various cancers with a very early age of onset. We are presenting a 41-year-old woman with right invasive ductal cancer and no family history of cancers, diagnosed with mosaic LFS confirmed with blood and skin punch biopsy samples. She was treated with neoadjuvant chemotherapy, mastectomy and sentinel node biopsy with completion axillary dissection. Adjuvant radiation was not recommended due to increased risk of secondary cancers. She also elected to undergo risk reducing contralateral mastectomy. Further research is warranted to determine the appropriate clinical management and surveillance strategies in patients with mosaic LFS as whether individuals with mosaic LFS have differing cancer risks in comparison to classic germline LFS is unknown.

INTRODUCTION

Li-Fraumeni syndrome (LFS) is an autosomal dominant condition caused by pathogenic variants in the TP53 tumor suppressor gene and characterized by a high lifetime risk of various cancers with very early age of onset [1, 2]. Cumulative cancer incidence among individuals with LFS is nearly 100% by age 70 [3]. Cumulative breast cancer incidence among women with LFS is up to 85% by age 60, which is comparable to the incidence associated with BRCA1 and BRCA2 pathogenic variants [3].

Very few cases of mosaic LFS have been reported [4–6]. Recent studies estimate that 14–38% of TP53 gene variants are due to spontaneous post-zygotic (mosaic) pathogenic variants, compared with <1% of variants in other hereditary cancer genes like APC, ATM, BRCA1 and BRCA2 [7, 8].

A diagnosis of LFS is made when an individual has a heterozygous germline pathogenic variant in the TP53 gene or all three of the following clinical criteria are met: a proband with a sarcoma diagnosed before age 45, a first-degree relative with any cancer diagnosed before age 45 and a first or second-degree relative with any cancer diagnosed before age 45 or a sarcoma diagnosed at any age [9].

To determine if an individual with a TP53 pathogenic variant has a rare mosaic form of LFS or the more common germline form of LFS, next-generation sequencing of a blood sample is used to calculate the variant allele frequency (VAF) of the specific TP53 variant [10]. The VAF is the percentage of sequence reads that match a specific DNA variant divided by the total number of sequence reads [11]. VAF is a measure of diploid zygosity, so heterozygous loci should be 50%, homozygous loci should be 100% and reference loci should be 0% [11]. In the case of LFS, the VAF for a specific TP53 mutation is in between the reference loci and heterozygous loci range (10–35%) rather than the expected VAF for heterozygous loci (50%). The altered VAF may suggest mosaicism because only some rather than all cells have a heterozygous genotype at the loci for the TP53 gene. Aberrant clonal expansion or clonal hematopoiesis needs to be distinguished from somatic mosaicism by additional testing [10].

CASE REPORT

A 41-year-old female with no family history cancer presented with a palpable right breast mass measuring 7 × 7 cm with distortion and skin dimpling.

Imaging showed 4-cm mass at right breast 6:00 2–5 cm from the nipple and axillary adenopathy that was categorized as BIRADS5. Biopsy showed grade 3 invasive ductal carcinoma that was strongly ER/PR positive (91%, 98%) and HER-2/neu negative (Group 5) with axillary nodal involvement.

Breast MRI demonstrated an irregular, spiculated, 3.8 × 8.9 × 3.8-cm mass and right axillary adenopathy. Staging scans showed no evidence of distant metastasis. Given the extent of local/regional disease, she was started on neoadjuvant dose dense doxorubicin and cyclophosphamide followed by weekly paclitaxel.

Genetic testing was done due to young age at diagnosis. Initial blood testing revealed a pathogenic variant in p53 present in 25–35% of cells. The patient's specific pathogenic variant was determined to be c.818G > A (p.Arg273His), which signifies the

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replacement of arginine with histidine at codon 273 of the TP53 protein. These results were suggestive of mosaic LFS. To confirm these results the patient underwent a skin biopsy, and analysis of the gDNA from skin fibroblasts demonstrated p53 mutation in 10–20% of the sampled tissues. The low variant allele frequency present in two tissue types confirmed the patient's mosaic LFS diagnosis. The initial (blood) sample was obtained prior to initiation of chemotherapy. The second (skin punch biopsy) sample was obtained after initiation of chemotherapy.

The patient had an excellent response to neoadjuvant chemotherapy with resolution of the breast mass and axillary adenopathy on MRI. A right total mastectomy and targeted axillary node dissection (intraoperative frozen section showed positive lymph nodes) and completion axillary node dissection was performed with plan for delayed reconstruction.

Pathology showed residual 1.5-cm high grade invasive ductal cancer with associated high grade ductal carcinoma in-situ with extensive intraductal component excised with negative margins, 2 out of 16 lymph nodes with micro-metastasis. Tumor receptors were repeated and interestingly were negative for ER, PR and HER-2/neu.

Adjuvant radiation was not recommended after weighing risk of radiation-induced cancers associated with LFS vs. local/regional recurrence risk. She received adjuvant capecitabine, then endocrine treatment was started. After discussing high risk screening versus contralateral risk reducing mastectomy, patient elected to undergo left mastectomy and underwent immediate reconstruction of left breast and delayed reconstruction of right breast.

DISCUSSION

Current guidelines recommend that women with LFS undergo a clinical breast examination twice a year and an annual breast MRI beginning at age 20. Patients may also consider risk-reducing bilateral mastectomy [1]. The Toronto Protocol additionally recommends extensive physical exams, annual whole-body MRI, annual brain MRI, annual dermatologic exam, endoscopy and colonoscopy at least every 5 years, and ESR, CBC, DHEA-sulfate and testosterone levels drawn every 4 months [1].

In patients with mosaic LFS, the possibility of future inheritance is unknown as there is no current test to determine whether an individual's germ cells contain the pathogenicTP53 variant. As a result, providers should educate patients about the possible inheritability of their syndrome and advise genetic counseling for their offspring. For patients who are diagnosed with LFS prior to childbearing, in vitro fertilization (IVF) and preimplantation genetic testing may be considered.

A diagnosis of LFS influences oncologic management [10]. Patients with LFS have an estimated 30% increased risk of radiation-induced secondary tumors so radiation therapy is avoided whenever possible [9, 12, 13]. The extent of this increased risk is now up for debate as a recent study found a much lower risk of radiation-induced malignancies in breast cancer patients with LFS (6%) than previously reported (30%), suggesting that radiation therapy may be a relative rather than absolute contraindication [14]. In patients who are candidates for breast conservation, mastectomy instead of lumpectomy with radiation should be considered.

CONCLUSION

Mosaic LFS is a newly discovered subtype and further research is warranted to determine the appropriate clinical management and surveillance strategies in these patients as whether individuals with mosaic LFS have differing cancer risks in comparison to classic germline LFS is unknown.

CONFLICT OF INTEREST STATEMENT

None declared.

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REFERENCES

1. Kratz CP, Achatz MI, Brugières L, Frebourg T, Garber JE, Greer MC, *et al.* Cancer screening recommendations for individuals with Li-Fraumeni syndrome. *Clin Cancer Res* 2017;**23**:e38–45.
2. Schon K, Tischkowitz M. Clinical implications of germline mutations in breast cancer: TP53. *Breast Cancer Res Treat* 2018;**167**: 417–23.
3. Mai PL, Best AF, Peters JA, DeCastro RM, Khincha PP, Loud JT, *et al.* Risks of first and subsequent cancers among TP53 mutation carriers in the National Cancer Institute Li-Fraumeni syndrome cohort. *Cancer* 2016;**122**:3673–81.
4. Prochazkova K, Pavlikova K, Minarik M, Sumerauer D, Kodet R, Sedlacek Z. Somatic TP53 mutation mosaicism in a patient with Li–Fraumeni syndrome. *Am J Med Genet A* 2009;**149A**:206–11.
5. Behjati S, Maschietto M, Williams RD, Side L, Hubank M, West R, *et al.* A pathogenic mosaic TP53 mutation in two germ layers detected by next generation sequencing. *PLOS ONE* 2014;**9**:e96531.
6. Zhang J, Walsh MF, Wu G, Edmonson MN, Gruber TA, Easton J, *et al.* Germline mutations in predisposition genes in Pediatric cancer. *N Engl J Med* 2015;**373**:2336–46.
7. Coffee B, Cox HC, Kidd J, Sizemore S, Brown K, Manley S, *et al.* Detection of somatic variants in peripheral blood lymphocytes using a next generation sequencing multigene pan cancer panel. *Cancer Genet* 2017;**211**:5–8.
8. Renaux-Petel M, Charbonnier F, Théry JC, Fermey P, Lienard G, Bou J, *et al.* Contribution of de novo and mosaic TP53 mutations to Li-Fraumeni syndrome. *J Med Genet* 2018;**55**:173–80.
9. Schneider K, Zelley K, Nichols KE, Garber J. Li-Fraumeni Syndrome. In: Adam MP, Ardinger HH, Pagon RA, *et al.*, eds. *GeneReviews®*. University of Washington, Seattle; 1993. (16 December 2021, date last accessed). http://www.ncbi.nlm.nih.gov/books/NBK1311/
10. Batalini F, Peacock EG, Stobie L, Robertson A, Garber J, Weitzel JN, *et al.* Li-Fraumeni syndrome: not a straightforward diagnosis anymore-the interpretation of pathogenic variants of low allele frequency and the differences between germline PVs, mosaicism, and clonal hematopoiesis. *Breast Cancer Res* 2019;**21**:107.
11. Strom SP. Current practices and guidelines for clinical next-generation sequencing oncology testing. *Cancer Biol Med* 2016;**13**: 3–11.
12. Heymann S, Delaloge S, Rahal A, Caron O, Frebourg T, Barreau L, *et al.* Radio-induced malignancies after breast cancer postoperative radiotherapy in patients with Li-Fraumeni syndrome. *Radiat Oncol* 2010;**5**:104.
13. Bougeard G, Renaux-Petel M, Flaman JM, Charbonnier C, Fermey P, Belotti M, *et al.* Revisiting Li-Fraumeni syndrome from TP53 mutation carriers. *J Clin Oncol* 2015;**33**:2345–52.
14. Le AN, Harton J, Desai H, Powers J, Zelley K, Bradbury AR, *et al.* Frequency of radiation-induced malignancies post-adjuvant radiotherapy for breast cancer in patients with Li-Fraumeni syndrome. *Breast Cancer Res Treat* 2020;**181**:181–8.